

This Listing and Amendment of the Claims supersedes all prior versions

LISTING AND AMENDMENTS OF THE CLAIMS:

1. (Currently Amended) A method ~~Method~~—for the determination of adrenomedullin release in a human, ~~fluids for diagnostic purposes, wherein comprising measuring the level in a biological fluid sample of said human of the mid-regional partial peptide (SEQ ID NO:3) of proadrenomedullin (mid-pro AM) which has the sequence of SEQ ID NO 3 and which consists of comprises-amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial peptide of proadrenomedullin in the said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring uses a monoclonal or polyclonal antibody which in each case is specific only to said partial peptide.~~

2. (Currently Amended) The method ~~Method~~—according to claim 261, wherein the mid-pro-AM in the biological fluid ~~fluids~~—is measured in an immunoassay which operates with at least one labeled antibody which specifically recognizes a sequence of mid-proAM.

3. (Currently Amended) The method ~~Method~~—according to claim 2, wherein the immunoassay is an assay with a solid phase-bound competitor for the mid-pro AM ~~analyte~~ and a labeled antibody (SPALT assay) or a sandwich assay (~~two-sided immunoassay~~), in which at least two antibodies which specifically bind to different

partial sequences of mid-proAM (SEQ ID NO: 3) are used.

4. (Currently Amended) The method ~~Method~~ according to claim ~~26~~¹, wherein the level of circulating mid-proAM (SEQ ID NO: 3) is determined and the biological fluid is a plasma.
5. (Currently Amended) The method ~~Method~~ according to claim 3, wherein both antibodies bind to a region of mid-proAM which extends from the amino acid 60 to the amino acid 94 of the pre-proAM.
6. (Currently Amended) The method ~~Method~~ according to claim 3, wherein all ~~the~~ antibodies are monoclonal and/or polyclonal.
7. (Currently Amended) The method ~~Method~~ according to claim 3, wherein all ~~both~~ antibodies are affinity-purified polyclonal antibodies.
8. (Currently Amended) The method ~~Method~~ according to claim 3, wherein for all said assays, one of the antibodies is obtained by immunization of an animal with an antigen which contains a synthetic peptide sequence which comprises the amino acids 69-86 of pre-proAM (SEQ ID NO: 4), and the other of the antibodies is obtained by immunization with an antigen which contains a synthetic peptide sequence which comprises the amino acids 83-94 of pre-proAM (SEQ ID NO: 5).

9. (Currently Amended) The method~~Method~~ according to claim 3, wherein for all said assays, one of the antibodies is labeled and the other antibody is bound to a solid phase, or one is labeled and not bindable to a solid phase and the other can be bound selectively to a solid phase.
10. (Currently Amended) The method~~Method~~ according to claim 3, wherein for all said assays, both the first and the second antibodies~~antibody~~ are present dispersed in ~~at the~~ liquid reaction mixture and ~~that a~~ first labeling component which is part of a labeling system based on fluorescence or chemiluminescence extinction or amplification is bound to the first antibody, and ~~at that the~~ second labeling component of ~~said this~~ labeling system is bound to the second antibody so that, after binding of both antibodies to the mid-proAM to be detected, a measurable signal which permits detection of the resulting sandwich complexes ~~in the measuring solution is generated~~.
11. (Currently Amended) The method~~Method~~ according to claim 10, wherein the labeling system comprises cryptate emission~~rare earth cryptates or chelates in combination with a fluorescent or chemiluminescent dye, in particular of the cyanine type~~.
12. (Currently Amended) The method~~Method~~ according to claim 1, further comprising wherein it is used for diagnosis of sepsis, for determination of its~~the~~ severity and prognosis and~~and~~ for therapy control accompanying the course of sepsis.

13. (Currently Amended) ~~The method~~ Method according to claim 12, wherein the determination of adrenomedullin release is carried out as part of a multiparameter determination in which at least one further parameter relevant for sepsis diagnosis is determined at the same time.

14. (Currently Amended) ~~The method~~ Method according to claim 13, wherein the further parameter or parameters relevant for sepsis diagnosis is or are ~~selected from the group consisting of anti-ganglioside antibodies, the proteins-procalcitonin, CA 125, CA 19-9, S100B, S100A proteins, LASP-1, soluble cytokeratin fragments, in particular CYFRA 21, TPS and/or soluble cytokeratin-1 fragments (sCY1F), the peptides-inflammin, and-CHP, a peptide prohormone other than pro-AM, other peptide prohormones, glycine-N-acyltransferase (GNAT), the carbamoylphosphate synthetase 1 or (CPS-1) and the C-reactive protein (CRP) or a fragment~~ fragments thereof.

15. (Currently Amended) ~~The method~~ Method according to claim ~~26~~, wherein the determination of adrenomedullin release is used for in the area of cardiac diagnosis of a cardiac disease.

16. (Currently Amended) ~~The method~~ Method according to claim 15, wherein the determination of adrenomedullin release is carried out in the course of a multiparameter determination in which further parameters relevant for cardiac diagnosis are also ~~determined at the same time.~~

17. (Currently Amended) ~~The method~~ Method according to claim ~~26~~1, wherein the determination of adrenomedullin release is used ~~for in the area of cancer diagnosis~~ of cancer.
18. (Currently Amended) ~~The method~~ Method according to claim 17, wherein the determination of adrenomedullin release is carried out in the course of a multiparameter determination in which further parameters relevant for cancer diagnosis are also ~~determined at the same time~~.
19. (New) A method for the determination of adrenomedullin release in a human, comprising measuring the level in a biological fluid sample of said human of the mid-regional partial peptide of proadrenomedullin (mid-pro AM) which has the sequence of SEQ ID NO 3 and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring uses a monoclonal or polyclonal antibody which in each case is specific to an epitope in said partial peptide sequence and not to any other epitope of pro-adrenomedullin.
20. (New) A method of claim 1 wherein said measuring is not accomplished using a competitive radioimmunoassay.

21. (New) A method for the determination of adrenomedullin release in a human, comprising measuring the level in a biological fluid sample of said human of the mid-regional partial peptide of proadrenomedullin (mid-pro AM) which has the sequence of SEQ ID NO 3 and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring is not accomplished using a competitive radioimmunoassay.

22. (New) A method for the determination of adrenomedullin release in a human, comprising measuring the level in a biological fluid sample of said human of the mid-regional partial peptide of proadrenomedullin (mid-pro AM) which has the sequence of SEQ ID NO 3 and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring is of the circulating level of said partial peptide circulating in a patient from whom said fluid is taken.

23. (New) A method of claim 22 wherein said measured level of said partial peptide in a fluid from a patient suffering from sepsis has an order of magnitude which is greater than the order of magnitude of 2X times said level in a healthy person.

24. (New) A method of claim 22 where said human is not suspected of suffering from sepsis.

25. (New) A method for the determination of adrenomedullin release in a human, comprising measuring the level in a biological fluid sample of said human of the mid-regional partial peptide of proadrenomedullin (mid-pro AM) which has the sequence of SEQ ID NO 3 and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring is by antibody sandwich assay employing at least two antibodies specific to epitopes in said partial peptide sequence.

26. (New) A method for the determination of adrenomedullin release in a human suspected of having a disease, other than sepsis, associated with an increased level of adrenomedullin release, comprising measuring the level of the mid-regional partial peptide of proadrenomedullin (mid-pro AM) which has the sequence of SEQ ID NO 3 and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of said mid-regional partial peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human.

27. (New) A method for the diagnosis of a disease other than sepsis which is

associated with an increased level of adrenomedullin release in a human, comprising measuring the level in a biological fluid of said human of the mid-regional partial peptide of proadrenomedullin (mid-pro AM) which has the sequence of SEQ ID NO 3 and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), and correlating said level of said mid-regional partial peptide with the presence of said disease.

28. (New) A method of claim 27 wherein said disease is a cancer or a cardiac disease.

29. (New) A method of claim 27 wherein said disease is a cardiac disease.

30. (New) An isolated polypeptide consisting of the amino acid sequence SEQ ID NO 3.

31. (New) A method of claim 19 wherein said measuring is not accomplished using a competitive radioimmunoassay.

32. (New) A method for the determination of adrenomedullin release in a human, comprising measuring the level in a biological fluid sample of said human of the mid-regional partial peptide of proadrenomedullin (mid-pro AM) which has the sequence of SEQ ID NO 3 and which consists of amino acids 45-92 of the complete preproadrenomedullin sequence (SEQ ID NO:1), said level of the mid-regional partial

peptide of proadrenomedullin in said biological fluid being indicative of the level of adrenomedullin release in said human, wherein said measuring is not accomplished using a radioimmunoassay requiring an extraction step.